

JP2003012686

**Title:  
PYRAZOLE DERIVATIVE**

**Abstract:**

**PROBLEM TO BE SOLVED:** To provide a pyrazole derivative useful as an agent for the prevention and/or treatment of diabetes or its pharmacologically permissible salt.

**SOLUTION:** The pyrazole derivative is expressed by general formula (I) [R<1>; is H, a substituted or unsubstituted lower alkyl or a substituted or unsubstituted lower alkoxy; R<4>; is a substituted or unsubstituted lower alkyl or a substituted or unsubstituted lower alkoxy; R<2>; is gluconopyranosyl group (the hydroxy group in the gluconopyranosyl group may be protected); and R<3>; is a substituted or unsubstituted aryl or a substituted or unsubstituted aromatic heterocyclic group]. The invention further relates to a pharmacologically permissible salt of the derivative.

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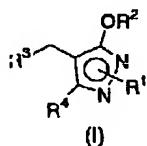
(54)【発明の名称】 ピラゾール誘導体

(57)【要約】

【課題】 本発明の目的は、糖尿病予防および/または治療剤として有用なピラゾール誘導体またはその薬理学的に許容される塩を提供することにある。

【解決手段】 一般式(I)

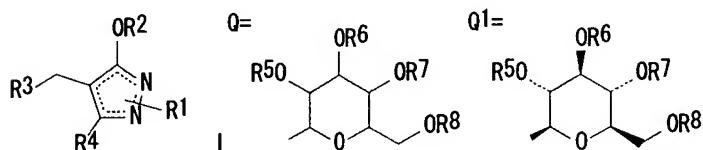
【化19】



[式中、R<sup>1</sup>は水素原子、置換もしくは非置換の低級アルキルまたは置換もしくは非置換の低級アルコキシを表し、R<sup>4</sup>は置換もしくは非置換の低級アルキルまたは置換もしくは非置換の低級アルコキシを表し、R<sup>2</sup>はグルコピラノシリル基（グルコピラノシリル基中の水酸基は保護されていてもよい）を表し、R<sup>3</sup>は置換もしくは非置換のアリールまたは置換もしくは非置換の芳香族複素環基を表す]で表されるピラゾール誘導体またはその薬理学的に許容される塩を提供する。

L1 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2003:36456 CAPLUS <<LOGINID::20060731>>  
 DN 138:90016  
 TI Preparation of 3-pyrazolyl glycosides for treatment of diabetes  
 IN Shirakura, Shiro; Ito, Yasuhiko; Kusaka, Hiroko; Kusaka, Hideaki;  
 Takeshita, Kenichi; Matsumoto, Yoshiko; Abe, Masayuki; Ota, Yoshihisa;  
 Nomoto, Yuji  
 PA Kyowa Hakko Kogyo Co., Ltd., Japan  
 SO Jpn. Kokai Tokkyo Koho, 16 pp.  
 CODEN: JKXXAF  
 DT Patent  
 LA Japanese  
 FAN. CNT 1

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OS	MARPAT 138:90016				
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AB 3-Pyrazolyl glycosides, in particular 3-pyrazolyl  $\beta$ -D-glucopyranosides [I]; R1 = H, (un)substituted lower alkyl or lower alkoxy; R4 = (un)substituted lower alkyl or lower alkoxy; R5-R8 = H, hydroxy-protecting group; when at least one of R5-R8 is a hydroxy-protecting group and R5-R8 is H and also R1 is (un)substituted lower alkyl or lower alkoxy, R3 is (un)substituted aryl or heterocycl; or when R5-R8 is H and R1 is H or lower alkyl, R3 is p-(un)saturated lower alkylsulfonylaryl, or substituted aryl, or (un)substituted aromatic heterocycl] or pharmacol. acceptable salts thereof are prepared. Also disclosed are preventives or remedies for diabetes or diabetes complications, blood sugar-lowering agents, or Na<sup>+</sup>-glucose cotransporter (sodium-glucose cotransporter) (SGLT) inhibitors containing the above compds. I as the active ingredients. Thus, to a solution of 4.00 g 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one and 14.78 g 2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl bromide in 300 mL MeCN was added 9.69 g K<sub>2</sub>CO<sub>3</sub> and stirred at room temperature for 3 days to give 58% 4-[(4-methylthiophenyl)methyl]-3-[(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)oxy]-5-trifluoromethyl-1H-pyrazole which (908 mg) was stirred with a mixture of 15 mL ethanol and 505 aqueous K<sub>2</sub>CO<sub>3</sub> at room temperature for 1 h to give 7% 4-[(4-methylthiophenyl)methyl]-3-[( $\beta$ -D-glucopyranosyl)oxy]-5-trifluoromethyl-1H-pyrazole (II). To a solution of 22 mg II in 1 mL MeOH was added 7 mg m-chloroperbenzoic acid and stirred at room temperature for 4 h to give 20% 4-[(4-methylsulfinylphenyl)methyl]-3-[( $\beta$ -D-glucopyranosyl)oxy]-5-trifluoromethyl-1H-pyrazole (III). In a SGLT inhibition assay, III showed IC<sub>50</sub> of 0.0466  $\mu$ M for inhibiting the uptake of [<sup>14</sup>C]AMG in proximal tubule epithelial cell lines (LLC-PK1). III at 1 mg/kg i.v. increased the urinary excretion of glucose from 502 $\pm$ 61  $\mu$ g/2 h (control) to 62,077 $\pm$ 10,456  $\mu$ g/2 h in male SLC SD rats.